Virginia Department of Health
Viral Hemorrhagic Fever: Guidance for Healthcare Providers
Key Medical and Public Health Interventions after Identification of a Suspected Case

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1. Epidemiology

Viral hemorrhagic fever (VHF) refers to a group of illnesses that are caused by viruses from the following 4 distinct families of viruses:

- *Arenaviridae* (e.g., Lassa virus, Lujo virus; New World viruses: Guanarito, Junin, Machupo and Sabia viruses)
- *Bunyaviridae* (e.g., Crimean-Congo hemorrhagic fever virus, Rift Valley Fever virus, Hantaan virus)
- *Filoviridae* (e.g., Ebola virus and Marburg virus)
- *Flaviviridae* (e.g., yellow fever virus, dengue virus, Omsk hemorrhagic fever virus, Kyasanur forest disease virus)

CDC also includes certain Paramyxoviridae viruses (e.g., Hendra virus and Nipah virus) in this group.

VHF viruses can cause a severe multisystem syndrome whereby the overall vascular system is damaged and the body's ability to respond is impaired. Other key characteristics of these viruses are the following:

- They are all RNA viruses, and are covered or enveloped in a fatty (lipid) coating.
- The viruses are geographically restricted to the areas where their host species live. Most occur in sub-Saharan Africa, Asia or focal areas of South America. Hantavirus is the only VHF that naturally occurs in the eastern United States.
- The survival of these viruses is dependent on a natural reservoir (e.g., animal or insect host). The natural reservoir depends on the specific virus involved, but can include ruminants (Crimean-Congo Hemorrhagic fever virus, Rift Valley Fever virus), bats (Marburg virus and potentially Ebola virus), or rodents (arenaviruses and hantaviruses).
- Humans are infected when they come into contact with infected hosts. In addition, vectorborne transmission can occur with several viruses via mosquitoes (Rift Valley Fever virus, dengue virus)

or ticks (Crimean-Congo Fever virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus). After transmission of the virus from the host, person-to-person transmission can occur with some of these viruses through direct contact with symptomatic patients, body fluids, cadavers or contaminated objects (Lassa virus, New World arenaviruses, filoviruses, Crimean-Congo hemorrhagic fever virus).

- Human cases or outbreaks of viral hemorrhagic fevers occur sporadically among people who live in or travel to endemic areas. The occurrence of outbreaks cannot be easily predicted.
- With a few noteworthy exceptions, there is no cure or established drug treatment for VHFs.

Many viruses that cause hemorrhagic fever (e.g., Ebola virus, Marburg virus, Lassa fever virus) are designated as a Category A bioterrorism agent (i.e., one that is easily disseminated or transmitted with a higher rate of mortality than a Category B agent) and a select agent, which means that it could be developed as a bioterrorism agent and that possession, use or transfer of these organisms requires registration with CDC or USDA. If VHF is suspected or confirmed, the local health department should be notified immediately so that a public health investigation can be initiated.

The epidemiology of several viruses causing VHF is described in more detail in Appendix 1.

2. Clinical Manifestations

The incubation period depends on the etiologic agent, but it can be as long as 21 days. For this reason, collecting a thorough history of travel and exposures within the 21 days before illness onset is critical.

Although some viruses cause relatively mild illnesses, other viruses cause severe, life-threatening disease. Signs and symptoms vary by disease, but, in general, include fever, headache, muscle pain, erythematous maculopaular rash on the trunk, vomiting, diarrhea, pharyngitis (arenavirus only), abdominal pain, bleeding (not related to injury) and retrosternal chest pain (arenavirus only). Vascular endothelial damage leads to shock and pulmonary edema. Liver injury is common. Signs or symptoms seen with specific viruses include renal failure (hemorrhagic fever with renal syndrome associated with hantaviruses), bruises (Crimean-Congo hemorrhagic fever), hearing loss and shock in newborns (Lassa fever), and spontaneous abortion and birth defects (Lassa fever).

The case-fatality rate varies by the etiologic agent. Appendix 1 includes case-fatality rates of several viruses causing VHF.

3. Laboratory Testing and Diagnosis

Notification when VHF is Suspected

If VHF is suspected, the healthcare provider should immediately report the case to the local health department per Virginia's disease reporting regulations. The local health department will discuss options for public health testing. If VDH approves public health testing, specimens may be sent to the Division of Consolidated Laboratory Services (DCLS). The health department will facilitate notification and shipment to DCLS. Specimens potentially containing a virus that causes VHF should never be shipped to DCLS without prior approval.

Laboratory Biosafety

Laboratory personnel **must** be alerted if VHF is suspected so that they can take appropriate precautions.

Diagnostic Testing
In general, diagnostic testing for viruses causing VHF requires high containment (e.g., Biosafety Level 3 or 4 practices). Testing is typically performed only at CDC. The one exception to this is that DCLS can perform preliminary PCR testing for Ebola virus, if CDC approves testing; confirmatory testing is conducted at CDC.

Multiple test types can be used to diagnose a VHF. The availability of the test depends on the agent. In general, testing includes enzyme-linked Immunosorbent Assay (ELISA) for antigen or antibody detection, viral isolation in cell culture for blood or tissues, detection of VHF-specific genetic sequence by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) from blood or tissues, and detection of VHF viral antigens in tissues by immunohistochemistry.

Sample Collection
General instructions for VHF testing at DCLS or CDC are shown in Table 1. For Ebola virus, refer to DCLS instructions that are available here.

Because of the highly infectious nature of these organisms, consultation with DCLS about specimen collection and handling is strongly recommended. The DCLS Emergency Officer can be reached 24/7 at 804-335-4617.

Case Definitions used by Public Health
The current CDC case definition for VHF is available here. Specific viruses described in the case definition include the following: Crimean-Congo Hemorrhagic fever virus, Ebola virus, Lassa virus, Lujo virus, Marburg virus, and New World Arenaviruses (Guanarito, Junin, Machupo and Sabia viruses). Note that a case definition is set of uniform criteria used to define a disease for public health surveillance. Case definitions enable public health to classify and count cases consistently across reporting jurisdictions, and should not be used by healthcare providers to determine how to meet an individual patient's health needs.

For Ebola, the CDC definition of a Person Under Investigation (PUI) is available here. Both clinical findings and relevant exposure within the 21 days before illness onset are required to meet the PUI definition and pursue public health testing.

Table 1. Sample collection instructions for testing suspected viral hemorrhagic fevers at DCLS or CDC*

Test and Estimated Turnaround Time	Acceptable Samples	Amount	Instructions
Serology (performed at CDC) Estimated turnaround time: 4-10 business days upon specimen receipt	Serum (red top tube or serum separator) or whole blood (purple, green, or blue top tube)	Minimum sample volume is 4 ml	The following specimen types may be submitted: • Serum drawn near admission with clots retained from red top tube • As late a serum as available • Convalescent serum drawn approximately 21 days after first specimen • Post-mortem heart blood Serum samples must be shipped with a cold pack, or on dry ice in a **plastic** tube. Clots and acute blood for virus isolation must be sent on dry ice in a **plastic** tube.
Immunohistochemistry (IHC, performed at CDC) Estimated turnaround time: 8 weeks upon specimen receipt	Lung, kidney, and spleen tissues are preferred. Other tissues that may be sent include lymph nodes, heart, pancreas, pituitary, brain, or liver.	Consult with DCLS	Specimen packaging requirements: • Paraffin blocks are preferred, particularly if death was not recent. • If paraffin blocks are not available, formalin-fixed tissues may be sent. • Ship paraffin blocks or formalin-fixed tissue at room temperature--do not freeze. • An autopsy or surgical report must accompany the specimen.
PCR/ Virus Isolation Estimated turnaround time: 4-10 business days upon specimen receipt (performed at CDC) Estimated turnaround time for Ebola RT-PCR testing at DCLS: 3-5 hours upon specimen receipt.	Preferred: whole blood (purple, yellow, or blue top tube), fresh frozen tissue. Serum can also be used if only sample available.	Minimum sample volume: 4 ml. Fresh frozen tissues should be at least $1cm^3$, except for biopsies.	Ship sample frozen on dry ice in a plastic tube. Do not freeze glass tubes.

*General instructions for viral hemorrhagic fever (VHF) are presented in this table; specific instructions for Ebola virus are available here. If VHF is suspected, notify the local health department immediately to discuss the case and laboratory testing. If VDH approves testing, specimens may be sent to the Division of Consolidated Laboratory Services (DCLS) with the DCLS Clinical Microbiology/ Virology Request Form; include the name of the test on the form. For questions about specimen collection, the DCLS Emergency Officer can be reached 24/7 at 804-335-4617.

4. Treatment

Patients with VHF should receive supportive therapy for symptoms and complications, but, in general, there is no other specific treatment or established cure. Supportive therapy includes maintenance of fluid and electrolyte balance, mechanical ventilation, dialysis, steroids (if adrenal involvement), and antibiotics for secondary bacterial infections.

Early treatment with ribavirin, an antiviral drug, can be effective for treating patients with Lassa fever, other Old World arenaviruses, and New World arenaviruses. Ribavirin might be effective for treating Crimean-Congo hemorrhagic fever, but more data are needed to evaluate this. Ribavirin is not effective against filoviruses or flaviviruses. Intravenous ribavirin can be obtained for compassionate use through FDA from Valeant Pharmaceuticals (Aliso Viejo, California). The healthcare provider should initiate the request to FDA at 301-796-1500 or, during after hours, at 866-300-4374, and should also simultaneously notify Valeant Pharmaceuticals at 800-548-5100, extension 5. Requesting ribavirin through the emergency investigational new drug process is explained on FDA's website.

Other experimental treatments, such as monoclonal antibody cocktails and antivirals, have been used in some patients, but there is limited evidence of their effectiveness on clinical outcome.

5. Postexposure Prophylaxis

Persons exposed to a virus that causes VHF, including close contacts of a patient with VHF, are recommended to be under postexposure surveillance for 21 days after the last known or potential exposure. Depending the risk of exposure, self-monitoring or active monitoring by public health might be recommended. In a 2002 paper by Borio et al, the Working Group on Civilian Biodefense did not recommend prophylactic antiviral therapy for persons exposed to any hemorrhagic fever viruses (including Lassa virus) in the absence of clinical illness; instead, the group recommended monitoring the exposed person for 21 days and, if symptoms suggestive of VHF develop or fever (≥101°F) are documented, ribavirin therapy should be initiated unless another diagnosis is confirmed (or the etiologic agent is known to be a filorvirus or flavivirus). Other researchers have suggested considering postexposure prophylaxis (PEP) with ribavirin for persons exposed to an arenavirus or bunyavirus, particularly if a high-risk exposure (e.g., needlestick injury) has occurred.

6. Vaccination

FDA-approved vaccines against VHF are not available in the United States with the exception of the yellow fever vaccine. A human vaccine for Kyasanur Forest Disease and an animal vaccine for Rift Valley Fever are used in endemic areas; in addition, there are investigational vaccines for Argentine hemorrhagic fever, Ebola virus disease, and Rift Valley fever.

7. Infection Control

The following infection control recommendations should be followed when caring for persons with suspected VHF:

- For Ebola virus disease, refer to CDC's infection control and prevention guidance. Note that, as of this writing, CDC has separate personal protective equipment (PPE) guidance depending on the status of the PUI and clinical presentation.
  - Infection Prevention and Control Recommendations for Hospitalized Patients with Known or Suspected Ebola Virus Disease in U.S. Hospitals
  - Donning and Doffing Personal Protective Equipment (PPE) for Evaluating Persons Under Investigation (PUIs) for Ebola Who Are Clinically Stable and Do Not Have Bleeding, Vomiting, or Diarrhea
  - Guidance on Personal Protective Equipment (PPE) To Be Used By Healthcare Workers during Management of Patients with Confirmed Ebola or Persons under Investigation (PUIs) for Ebola who are Clinically Unstable or Have Bleeding, Vomiting, or Diarrhea in U.S. Hospitals, Including Procedures for Donning and Doffing PPE
  - Interim Guidance for Environmental Infection Control in Hospitals for Ebola Virus
- For VHF caused by other viruses, including Lassa, Marburg, and Crimean-Congo fever viruses, patients should be isolated in a private room and on Standard, Contact, and Droplet precautions for the duration of illness (Siegel JD, et al 2007 and the corresponding Appendix A updates.
  - Although transmission by the airborne route has not been established, Airborne Precautions may be initiated for patients if bioterrorism is suspected or for patients undergoing airborne-generating procedures (e.g., aerosolized or nebulized medication administration, diagnostic sputum induction, bronchoscopy, airway suctioning, endotracheal intubation, positive pressure ventilation via face mask and high frequency oscillatory ventilation). Airborne Precautions entail placement of patient in a negative pressure isolation room with 6-12 air changes per hour, air exhausted directly to the outdoors or passage through a high-efficiency particulate air (HEPA) filter before recirculation, and door kept closed.
  - Staff should be trained on the correct use of PPE and demonstrate proficiency in donning and doffing PPE before actual patient care. A trained observer of donning and doffing PPE is strongly recommended.
  - PPE should include gloves and fluid-resistant or impermeable gown, face/eye protection with masks, goggles or face shields. Additional PPE, including double gloves, leg and shoe coverings may be used. When performing aerosol-generating procedures, use a NIOSH-certified, fit-tested N-95 or higher respirator.
  - A private patient room is preferred. If multiple patients with viral hemorrhagic fever are in a health care facility, they should be cared for in the same part of the hospital to minimize exposures to others.
  - Nonessential staff and visitors should be restricted from entering the room of patients with suspected VHF. A log of persons entering the patient's room should be maintained.
  - Before exiting the room of a patient with suspected VHF, safely remove and dispose of all protective gear, and clean and disinfect shoes that are soiled with body fluids as described in the section on environmental infection control below.
  - To prevent percutaneous injuries, needles and other sharps should be used and disposed of in accordance with recommendations for Standard Precautions.
  - Healthcare workers should strictly adhere to hand hygiene.
  - Healthcare workers should use barrier precautions to prevent skin or mucous membrane exposure of the eyes, nose, and mouth with patient blood, other body fluids, secretions (including respiratory droplets), or prevent contact with items or environmental surfaces that may be soiled.
  - If the patient requires a surgical or obstetric procedure, consult the local health department and Infection Preventionist regarding appropriate precautions for these invasive procedures.

8. Decontamination

- Environmental surfaces or inanimate objects contaminated with blood, other body fluids, secretions, or excretions should be cleaned and disinfected using standard procedures.
  - For cleaning and disinfection for Ebola virus, refer to CDC's Ebola guidance for clinicians.
- Disinfection can be accomplished using a U.S. Environmental Protection Agency (EPA)-registered hospital disinfectant or a 1:100 daily dilution of household bleach (1/4 cup bleach to 1 gallon water). For grossly soiled surfaces, (e.g., vomitus or stool), use a 1:10 dilution of household bleach.
- Soiled linens should be incinerated, autoclaved or placed in double, clearly labeled leak-proof bags at the site of use and discarded. Hospital housekeeping staff and linen handlers should wear appropriate PPE when handling or cleaning potentially contaminated material or surfaces.
- Liquid medical waste such as feces and vomitus can be disposed of in the sanitary sewer following local sewage disposal requirements. Care should be taken to avoid splashing when disposing of these materials.
- When discarding solid medical waste (e.g., needles, syringes, and tubing) contaminated with blood or other body fluids from VHF patients, contain the waste with minimal agitation during handling. Properly contained wastes should be managed according to existing local and state regulations for ensuring health and environmental safety during medical waste treatment and disposal. On-site treatment of the waste in an incinerator or a gravity displacement autoclave for decontamination purposes will help to minimize handling of contaminated waste. Alternatively, off-site medical waste treatment resources may be used.

9. Postmortem Practices

If VHF is suspected as a cause of death, the district Office of the Chief Medical Examiner should be notified immediately. Contact with cadavers has been implicated as a source of transmission in previous VHF outbreaks. Prompt burial or cremation of the deceased, with minimal handling, is recommended. No embalming should be done. Remains should be wrapped in sealed leak-proof material and cremated or buried promptly in a sealed casket. If an autopsy is necessary, it should be performed only after consultation with and approval from VDH and CDC and by specially trained persons using VHF-specific barrier precautions, HEPA-filtered respirators and negative-pressure rooms.

10. Public Health Measures

- Suspected or confirmed VHF cases should be reported immediately to the local health department.
- Laboratory specimens should be sent to the state public health laboratory (DCLS) for preliminary testing of agent and/or shipment to the CDC after VDH consultation and approval. For questions about specimen collection, the DCLS Emergency Officer can be reached 24 hours a day/7 days a week at 804-335-4617.
- Designated public health authority should begin an epidemiologic investigation.
  - Collect detailed information from the patient to attempt to identify the source of the exposure.
  - Investigate contacts of the patient for compatible illness to investigate a potential common exposure.

- Implement control measures to prevent disease and additional exposures. Monitor close contacts of VHF patients 21 days. For laboratorians who handled infectious specimens or others who were potentially exposed before identification as a VHF, postexposure monitoring might be recommended based on a risk assessment.
- VDH will work with the CDC, Federal Bureau of Investigation (FBI) and other state or federal agencies as necessary.

11. References and Resources

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12. Appendix 1: Epidemiology and clinical manifestations of specific viruses causing viral hemorrhagic fever by virus family

Note: Other hemorrhagic fever viruses exist in these categories; however, the viruses that pose the most serious risk as biological weapons are the following: arenaviruses (Lassa virus, New World arenaviruses), bunyaviruses (Rift Valley fever virus), filoviruses (Ebola virus, Marburg virus), and flaviviruses (yellow fever virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus). Dengue virus, Crimean-Congo hemorrhagic fever viruses and hantaviruses are considered less likely to be used as biological weapons (Borio, et al 2002). The role of other hemorrhagic fever viruses as potential weapons is not known.

Arenaviruses

1) Lassa Fever

- Organism: Lassa virus
- Natural reservoir: multimammate rat (*Mastomys* rodent)
- Person-to-person transmission: Yes
- Occurrence: Endemic in Benin, Ghana, Guinea, Liberia, Mali, Nigeria, and Sierra Leone and probably in other West African countries. An estimated 100,000 – 300,000 infections, including approximately 5,000 deaths, occur annually. In some areas of Sierra Leone and Liberia, it is known that 10%–16% of people admitted to hospitals every year have Lassa fever.
- Incubation period: 6–21 days
- Signs and symptoms: Most infections (80%) are asymptomatic or mild with slight fever, general malaise and weakness, and headache. In 20% of infections, disease is severe with multisystem involvement and hemorrhaging (e.g., in gums, eyes, or nose), respiratory distress, vomiting, facial swelling, pain in the chest, back, and abdomen, and shock. Neurological symptoms (e.g., hearing loss, tremors, and encephalitis) can be present. Pregnant women are more likely to develop severe disease and fetal loss occurs in >80% of cases. Deafness occurs in ~25% of patients who survive; half of these patients regain partial hearing after 1–3 months.
- Case-fatality rate: ~1% of all infections; ~15%–20% among hospitalized patients

2) New World Arenaviruses

- Organism: multiple (including Machupo, the cause of Bolivian hemorrhagic fever; Junin, the case of Argentine hemorrhagic fever; Guanarito, the cause of Venezuelan hemorrhagic fever; Sabia, the cause of Brazilian hemorrhagic fever)
- Natural reservoir: rats and mice
- Person-to-person transmission: Yes
- Occurrence: Depends on the virus and the host, but primarily limited to certain areas in Argentina, Bolivia, Brazil, and Venezuela
- Incubation period: Depends on the virus, but typically 6–14 days (range 5–21 days)
- Signs and symptoms: Asymptomatic infections occur. If signs and symptoms are present, they include fever, headache, anorexia, malaise, muscle pain, with pain especially in the lower back; other symptoms might include nausea, dizziness, abdominal pain, vomiting, diarrhea, sore throat, flushing of the head and torso, or generalized lymphadenopathy. Most patients improve after a week or two, but about 1/3 of untreated cases become severe and life-threatening. Petechiae and ecchymosis on the skin or gums, bleeding from the vagina or gastrointestinal tract, and neurologic symptoms might be present.
- Case-fatality rate: 15%–30% in untreated patients

Bunyaviruses

1) Rift Valley Fever (RVF)

- Organism: Rift Valley fever virus
- Natural reservoir: Ruminants (e.g., cattle, sheep and possibly wild ruminants), rats in some areas
- Person-to-person transmission: No
- Occurrence: Rift valley fever was first reported in livestock in Kenya's Rift Valley in the early 1910s. RVF is generally found in eastern and southern Africa, but the virus exists in most of sub-Saharan Africa, including West Africa and Madagascar. In September 2000, a RVF outbreak was reported in Saudi Arabia and subsequently, Yemen. This outbreak represented the first identified cases outside Africa.
- Incubation period: 2–6 days
- Signs and symptoms: Most commonly, people with RVF have either no symptoms or a mild illness associated with flu-like fever, pain in the muscle and joints, and headache. Most patients recover within one week after onset of illness. Some patients (8–10%) develop much more severe symptoms, including the following:
  - Ocular form: blurred and decreased vision that occurs 1–3 weeks after illness onset and might resolve within 10–12 weeks
  - Meningoencephalitis form: headaches, memory loss, hallucinations, confusion, disorientation, vertigo, convulsions, lethargy and coma. This form occurs in less than 1% of patients and presents 1–4 weeks after initial symptoms appear. Although death is rare, neurological deficits often persist.
  - Hemorrhagic fever form: which occurs in <1% of patients, may begin with jaundice and other signs of liver impairment, followed by vomiting blood, bloody stool, or bleeding from gums, skin, nose, and injection sites. These symptoms appear 2–4 days after initial onset and death usually occurs 3–6 days later.
- Case-fatality rate: <1% overall and ~50% among those with hemorrhagic fever form

Filoviruses

1) Ebola Virus Disease (EVD)

- Organism: Ebola virus
- Natural reservoir: Unknown, presumed to be fruit bats
- Person-to-person transmission: Yes
- Occurrence: first identified in 1976**;** since then, sporadic outbreaks have been identified in Africa, primarily in sub-Saharan countries. The largest EVD outbreak occurred in 2014–2016 in West Africa.
- Incubation period: 8–10 days (range 2–21 days)
- Signs and symptoms: Fever, fatigue, headache, joint and muscle aches, and sore threat. These are followed by diarrhea, vomiting, and symptoms of impaired kidney and liver function, and in some cases bleeding inside and outside the body.
- Case-fatality rate: ~50% overall and 25%–90% in outbreaks

2) Marburg Hemorrhagic Fever (MHF)

- Organism: Marburg virus
- Natural reservoir: fruit bat (*Rousettus aegypticus*)
- Person-to-person transmission: Yes
- Occurrence: First identified in 1967 when outbreaks of hemorrhagic fever occurred simultaneously in laboratories in Germany and Yugoslavia. Countries in which MHF has been identified include Uganda, Zimbabwe, the Democratic Republic of the Congo, Kenya, and Angola. A few cases outside of Africa have been identified and were related to either laboratory exposure or importation after travel to Africa.

- People who have close contact with a human or non-human primate infected with the virus are at risk (includes laboratory or quarantine facility workers) for developing the disease. In addition, hospital staff and family members who care for patients with the disease are at risk if they do not use proper barrier nursing technique.
- Incubation period: 5–10 days (range 2–21 days)
- Signs and symptoms: symptom onset is sudden and marked by high fever, severe headache, and severe malaise. Muscle aches and pains are common. On the third day, severe diarrhea, abdominal pain, nausea, and vomiting can begin. A maculopapular rash, most prominent on the trunk (chest, back, stomach), might occur 2–7 days after initial symptom onset. Symptoms become increasingly severe and can include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, severe hemorrhaging (which occurs 5–7 days after onset), and multi-organ dysfunction. Central nervous system involvement manifests as confusion, irritability, and aggression. Orchitis, which can occur during the late stages of infection, has occasionally been reported.
- Case-fatality rate: 23%–90%

Flaviviruses

1) Yellow Fever

- Organism: Yellow fever virus (YFV)
- Natural reservoir: nonhuman and human primates
- Person-to-person transmission: Yes (also vectorborne transmission via infected mosquitoes, primarily *Aedes* or *Haemagogus* spp.)
- Occurrence: Endemic in parts of Africa (particularly sub-Saharan West Africa) and Central and South America. Occurrence depends on transmission cycle present in the area. With the sylvatic (jungle) transmission cycle, transmission occurs between nonhuman primates and mosquitoes in the forest canopy in tropical regions of Africa and Latin America. With the intermediate (savannah) transmission cycle, transmission occurs via various *Aedes* spp., humans and nonhuman primates in humid and semihumid areas of Africa. With the urban transmission cycle, transmission occurs between humans and mosquitoes (primarily *Aedes aegypti*) in parts of Africa, particularly West Africa.
- Incubation period: 3–6 days
- Signs and symptoms: Most infections are asymptomatic. Symptoms, if present, include fever, chills, headache, backache, general muscle pain, prostration, nausea, and vomiting. Some patients might just experience mild, febrile illness. In approximately 15% of cases, there is a brief remission of symptoms lasting hours to a day followed by the recurrence of initial symptoms and progression to jaundice and hemorrhagic symptoms. Leukopenia (most pronounced around Day 5 of infection), leukocytosis (usually in second week of infection), elevated liver enzymes, abnormal clotting factors, albuminuria and anuria may be seen as a result of liver and renal failure.
- Case-fatality rate: 30%– 60% for those with severe disease

2) Kyasanur Forest Disease (KFD)

- Organism: Kyasanur Forest disease virus (KFDV)
- Natural reservoir: Rodents, bats and other small mammals; monkeys appear to be amplifying hosts; arthropod vector: ticks (*Haemaphysalis spinigera*)
- Person-to-person transmission: No
- Occurrence: KFDV was identified in 1957 from a sick monkey from the Kyasanur Forest in India. Since then, approximately 400–500 human cases per year have been reported.
- Incubation period: 3–8 days

- Signs and symptoms: Symptoms begin suddenly with fever, chills, and headache, followed in 3–4 days with severe muscle pain, vomiting, gastrointestinal symptoms, and bleeding. Abnormally low blood pressure and low platelet, red blood cell, and white blood cell counts might occur. Some patients recover without complication after 1–2 weeks. However, some patients (10–20%) experience a second wave of symptoms at the start of the third week that include fever and neurological manifestations, such as severe headache, mental disturbances, tremors, and vision deficits.
- Case–fatality rate: 3%–5%

3) Omsk hemorrhagic fever (OHF)

- Organism: Caused by Omsk hemorrhagic fever virus (OHFV)
- Natural reservoir: rodents (including muskrats and voles); arthropod vector: ticks (*Dermacentor reticulatus*, *Dermacentor marginatus*, *Ixodes persulcatus)*
- Person-to-person transmission: No
- Occurrence: OHF was first described between 1945 and 1947 in Omsk, Russia from patients with hemorrhagic fever, and is endemic in the western Siberia region.
- Incubation period: 3–8 days
- Signs and symptoms: The symptoms begin suddenly with fever, chills and headache, followed in 3–4 days with severe muscle pain, vomiting, gastrointestinal symptoms, and bleeding. Some patients might experience abnormally low blood pressure and low platelet, red blood cell, and white blood cell counts. After 1–2 weeks of symptoms, some patients recover without complication. Other patients might experience a second wave of symptoms at the beginning of the third week that include fever and encephalitis.
- Case-fatality rate: <1%–3%